REMARKS

The Examiner again points to the Merriam-Webster Dictionary definition of "Mineralize". Generally speaking, terms are given their plain meaning, unless the term has a particular meaning within the specification and/or the inventor has chosen to be his/her own lexicographer and give the term a special meaning. Applicant's meaning of the term mineralize should be read in the context of the phrase "mineralized collagen matrix", the meaning of which can easily be determined from applicants' disclosure.

The specification clearly shows that the mineralized collagen matrix is constructed in the form of layers. At least one of the layers comprises a composite of mineralized collagen fibrils, amorphous calcium phosphate and crystalline hydroxyapatite. Crystals of hydroxyapatite having a length of about 300 to 500 nm are present on and between the collagen fibrils. Based on the many descriptions of the microscopic examinations found in applicants' specification, the meaning of the phrase "mineralized collagen matrix" is more than sufficiently clear to one skilled in the art. Thus, one skilled in the art of would not look to a general-purpose dictionary meaning of "mineralized", particularly for a biomedical definition of "mineralized collagen matrix". Applicants' consistently use the phrase "mineralized collagen matrix" in the context of a bone analogous coating.

Rejections under 35 USC §112

Claims 1, 3-8, 10-19, 21,23-25 and 27 stand rejected under 35 U.S.C. 112, first paragraph and claims 2-3 and 23 stand rejected under 35 U.S.C. 112, second paragraph. The rejection is respectfully traversed.

Support for the recitation of "at least one of said layers comprises a composite of mineralized collagen fibrils, amorphous calcium phosphate and crystalline hydroxyappatite" can be found, for example, in original claims 1 and 3 and the specification at page 5, lines 30-38 which reads as follows:

"The mineralized collagen matrix is constructed in the form of layers. This has the advantage that by means of this the production of graded layers having a varying degree of mineralization of the collagen matrix is also possible. The preferred overall thickness of the matrix coating is about 0.04μm - 150 μm, especially about 3-8 μm. The preferred range for the typical dimensions of the hydroxyapatite crystals is about 300- 500 nm in length and 50-60 nm in diameter." (emphasis added)

Clearly use of the plural form "layers" in this passage provides support for a device comprising more than one layer comprising mineralized collagen and a calcium phosphate phase (used to mineralize the collagen). Since the calcium phosphate phase may contain amorphous calcium phosphate and hydroxyapatite (see, for example, page 6, 1st paragraph), the existence of more than one layer, as claimed in pending claim 1, is unambiguously described in the specification.

Thus, it is respectfully requested that the rejections under 35 U.S.C. 112 be withdrawn.

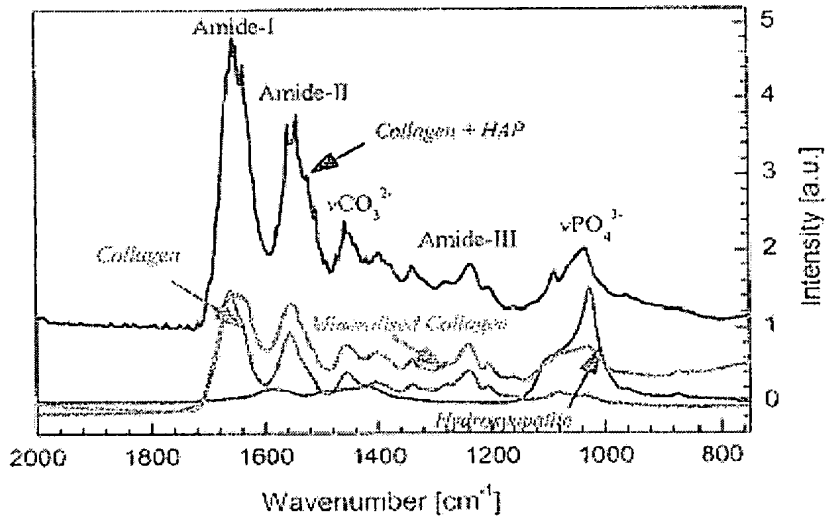
Rejections under 35 USC §103

As previously noted, there is a considerable difference between the structure of a simple mixture of collagen and calcium phosphate or hydroxyapatite, respectively, and the structure of a mineralized collagen matrix.

As can be seen in previously presented page 173 of Lehninger "Principles of Biochemistry", collagen is a rod-shaped molecule of about 3,000 Å long (300 nm) and 15 Å thick. In order to form bone analogous structures of interconnected layers, the calcium phosphate crystallite growth has to occur on and between the collagen fibrils. Thus, in bone analogous structures the hydroxyapatite crystals must be small enough to interact within the collagen fibrils, which have a size of about 0.3 μm or 3000 Å. Using hydroxyapatite crystals of a size much larger than collagen fibrils would result in domination of the mineral component, thereby creating a simple admixture of the collagen into the mineral matrix.

To illustrate the difference between a simple admixture of collagen and hydroxyapatite, on the one hand, and mineralized collagen according to the invention, on the other hand, Applicants present the following Fourier Transform Infrared (FTIR) spectra: (Figure 1).

Figure 1



This figure shows the FTIR spectra of

a) collagen (green curve),

b) hydroxyapatite (red curve),

c) a mixture of collagen and hydroxyapatite ("Collagen + HAP"; blue curve) which was manufactured by mixing hydroxyapatite particles and collagen and subsequent freeze-drying according to a process similar to that described in US 5,246,457 and

d) a mineralized collagen matrix according to the invention (cyan curve).

As can be clearly seen from the FTIR spectra, especially from the position of the amide-I band (C=O stretching vibration; here around 1650 to 1660 cm^{-1}), the relative intensity between the amide-I and the amide-11 band (N-H bending vibrations coupled with C-N stretching vibrations;

around 1550 cm") and the phosphate stretching vibration (between 1000 and 1150 cm^{-1}), the spectrum of the mixture of collagen and hydroxyapatite (blue curve) represents merely an addition of the single spectra of collagen (green curve) and hydroxyapatite (red curve). This is due to a lack of interactions of hydroxyapatite and collagen in a mixture of both compounds.

On the other hand, a mineralized collagen matrix according to the invention (cyan curve) shows a markedly different spectrum than collagen (green curve). The higher the grade of mineralization of the collagen matrix, the broader the amide-I band becomes. Concomitantly, the maximum of the amide-I band shifts to lower wave numbers (from about 1659 to 1656 cm^{-1}). This is generally considered to be due to a higher degree of hydrogen bonds within the material and is indicative of the changed secondary structure of the collagen matrix due to mineralization.

Another molecular structural explanation of the amide-I band shift is a decreasing electron density between the carbon and the oxygen of the C=O bond due to the incorporation of phosphate and calcium ions. Further, the more energetically different states of the C=O bonds of the mineralized collagen matrix exist, the broader the amide-I band becomes. The energetically different states also arise by interactions of collagen with positively (calcium) and negatively charged ions (phosphate) during mineralization.

Normal non-mineralized collagen, hydroxyapatite and the mixture of both show sharp bands clearly differing from the broad amide-I band of a mineralized collagen matrix according to the invention. Further, the ratio between the intensity of the amide-I band and the intensity of the amide-II band changes significantly during the mineralization process of collagen. As is evident from Figure 1, the amide-I to amide-II ratio remains almost constant between collagen (green curve) and a mixture of collagen and hydroxyapatite (blue curve). However, the relative intensity of the amide-II band is much higher in case of a mineralized collagen matrix according to the invention. By mineralization the peptide bonds of collagen become much more prone to N-H bending vibrations and C-N stretching vibrations.

Additionally, as can be seen from Figure 2 below, the FTIR spectrum of a mineralized collagen matrix much more closely resembles the spectrum of bone than that of normal non-mineralized collagen.

Figure 2

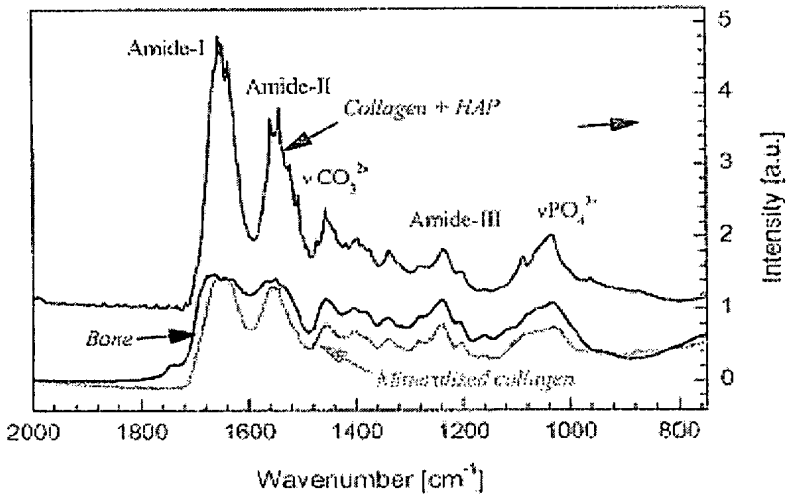


Figure 2 shows the FTIR spectra of

a) a mixture of collagen and hydroxyapatite ("Collagen + HAP"; blue curve) which was manufactured by mixing calcium phosphate particles and collagen and subsequent freeze-drying according to a process similar to that described in US 5,246,457,

b) bone (black curve) and

c) a mineralized collagen matrix according to the invention (cyan curve).

As can be clearly seen from the FTIR spectra of Figure 2, bone (black curve) shows a broad amide-I band having sub-maxima, a fact also known from literature. The reason for this broad amide-I band can be seen in many different states of collagen existing in bone material in parallel. These different states are detected by FTIR spectroscopy integrally.

Besides the impact of collagen molecules and fibrils in different mineralization states, it is believed that such a broad amide-I band is also due to conformational changes of the collagen by mineralization, particularly due to a smaller cross striation (changing from 67 to 64 nm).

The amide-I to amide-II intensity ratio is almost 1:1 in the case of bone material.

By comparing the spectra of bone and of a mineralized collagen matrix, it is apparent that these spectra are extremely similar. On the other hand, both the spectra of normal collagen and of a mixture of collagen and hydroxyapatite are signifcantly different from both the spectrum of bone and from the spectrum of mineralized collagen matrix.

Thus, the claimed metallic implant is coated with a mineralized collagen matrix that as noted above is structurally very different from a simple admixture of collagen and hydroxyapatite as disclosed or derivable from prior art. The claimed mineralized collagen matrix is constructed in the form of layers that comprises a composite of mineralized collagen fibrils, amorphous calcium phosphate and crystalline hydroxyapatite crystals having a length of about 300 to 500 nm.

With regard to the layers, at page 14 of the Office Action, it is the Examiner's position that collagen in combination with mineral components implicitly tends to separate into phases or layers. The Examiner cites US Patent 5,543,441, column 3 line, 66 - column 4, line 5, to support her position. However, this disclosure actually further supports the inventiveness of the claimed invention. As discussed above, the present invention is not just a combination of collagen and mineral components, but is a mineralized collagen matrix, having a clearly distinguishable structure from that of a mere combination of collagen and hydroxyapatite.

Claims 1, 4, 8, 10-16, 18-19, 21, 23-25, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 11-047259 in view of Constantz et al (5,279,831) optionally

in further view of Lussi et al (5,167,961).

JP 11-047259 teaches an implant coated with a "highly crystalline hydroxyapatite of which the amorphous calcium phosphate content is extremely small." See the abstract of JP'259. As the Examiner notes JP 11-047259 "does not teach the particle size of HA or collagen." Thus, JP 11-047259 is silent regarding hydroxyapatite crystals having a length of about 300 to 500 nm (i.e., 0.3 to 0.5 μm), and the presence of collagen.

Additionally, JP 11-047259 is silent regarding a coated metallic implant with an outer layer of a bone analogous coating comprising a collagen matrix, which is constructed in layers. The implant coatings of JP 11-047259 are not constructed in the form of layers. The reference is particularly silent with respect to a least one layer of an implant coating comprising a composite of mineralized collagen fibrils, amorphous calcium phosphate and crystalline hydroxyapatite.

At page 6, the Examiner asserts "it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of JP 11-047259 and Constantz et al and further add collagen to the hydroxyapatite coating. " Further with regards to the motivation for such a combination of teachings, the Examiner argues that "Constantz teaches a HA coating composition that may further comprise collagen and growth factors to enhance bone growth." However, Constantz et al. (US 5,279,831) does not make up for the deficiencies of JP 11-047259 discussed above.

Constantz et al. teaches a hydroxyapatite coating for prosthesis. The coatings of Constantz et al. may be combined with a wide variety of materials, such as collagen, bone growth factors, such as TGF-B, bone molphogenetic factor, combinations thereof or the like. These factors may be included in the reaction mixture or in a storage solution (column 5, line 67 to column 6, line 6). But by combining JP 11-047259 and Constantz et al., a skilled worker would arrive at a substrate coated by a coating consisting of a simple mixture of hydroxyapatite (with extremely small amounts of amorphous calcium phosphate) and collagen. See line (c) in Figure 1 above. The combined teachings would not lead a skilled worker to a layered structure of a

mineralized collagen matrix. This is especially true since Constantz et al. does not teach how to mineralize the collagen: The only teaching in Constantz with regards to collagen is at column 5, line 67 to column 6, line 6 where it is stated that "These factors may be included in the reaction mixture or in a storage solution".

Furthermore, with regard to crystal size, the range of crystal size disclosed by Constantz et al. is so broad (10 nm to 20 000 nm) as to render it meaningless. As noted above, in bone analogous structures the hydroxyapatite crystals must be small enough to interact within the collagen fibrils, which have a size of about 0.3 μm or 300 nm. Using hydroxyapatite crystals of a size much larger than collagen fibrils would result in domination of the mineral component, thereby creating a simple admixture of the collagen into the mineral matrix. Thus, if a skilled worker were to choose a hydroxyapatite crystal particle from within the majority of Constantz's range (i.e., 10 nm to 20 000 nm) the particle size would be too large. This would result in domination of the mineral component by the hydroxyapatite crystals and thus create the formation of a simple admixture of collagen and hydroxyapatite. There is nothing within Constantz to direct a skilled worker to choose a crystal size of 300 to 500 nm. Furthermore, since Constantz et al does not disclose any hint towards a mineralization of collagen, a skilled worker using hydroxyapatite crystals in the 10 nm to 20 000 nm size range would form a simple mixture of hydroxyapatite with other materials regardless of the crystal size chosen. Thus, the claimed crystal size of 300 to 500 nm within a layered mineralized collagen matrix is not obviously derivable from Constantz et al. and/or JP '259.

Lussi et al. (US 5,167,961) teaches a process for the preparation of high purity bone mineral wherein the organic matter in degreased bone is degraded and solubilized. The bone mineral is heated in air at temperatures between 250°C and 600°C. In Example 5 at col. 7, samples of materials were heated at very high temperatures i.e., between 600°C. and 800°C . The samples were analyzed and the results are summarized in Table 1 where it can be seen that the samples heated to 700°C resulted in crystal size of approx. 100-300 nm. The samples heated to 800°C resulted in crystal size of approx. 100-400 nm.

Contrary to the Examiners assertion, Lussi does not teach that all of the particle sizes as disclosed in Table 1 are beneficial. In fact, Lussi teaches the opposite. At col. 1, lines 42-59 it is stated:

> "The temperatures needed during calcination for the incineration of the organic constituents of the bones are rather high. This leads to extensive recrystallization of the mineral part with formation of much coarser crystals The so formed material exhibits a small specific surface and is not superior to any chemically precipitated hydroxylapatite.
>
> It should be emphasized that bone mineral which has been subjected to a treatment which results in significant increase in crystal size is much less readily remodelled on implantation since osteoclasts and osteoblasts cannot readily perform on such large crystals the dual function of mineral resorption and generation of new bone. Such implanted inserts may thus remain unchanged indefinitely eventually giving rise to undesirable effects. On the other hand, many synthetic tricalcium phosphate products tend to be resorbed too rapidly for osteoblasts to regenerate new bone. "

Furthermore, at col. 3 lines 58-64 Lussi states:

> "The final and essential step in the treatment of the bone mineral consists of dry heating to temperatures between 250°C and 600°C, preferably not greater than 550°C., more preferably between 350°C. and 500°C, for several hours. The higher temperatures are more effective in removing contaminants but tend to increase the risk of recrystallization with consequent increase of crystal size."

Clearly, the disclosure of Lussi regarding HA particle size would lead one skilled in the art away from the particle size asserted in applicants' claims.

Additionally, a skilled worker confronted with the problem of manufacturing a synthetic implant coating for metallic implants would never have taken Lussi et al. into account as being potentially relevant to solve his/her problem. Lussi et al. is not analogous art. Lussi does not teach implant coatings but instead, as mentioned above, is simply concerned with the preparation of high purity bone mineral wherein the organic material in bone is degreased, solubilized and removed.

Thus, even if a skilled worker would look to non-analogous art and consider Lussi et al., they would conclude that the crystal sizes disclosed by Lussi et al. would not be suitable. Furthermore, even if a skilled worker ignored the teaching away and choose to use the larger particles sizes disclosed in Table 1, they would form a simple admixture of hydroxyapatite with other materials and, as discussed in detail above. Neither JP '259, Constanz nor Lussi et al. disclose or suggest a mineralised collagen matrix constructed in the form of layers, whereby at least one of said layers comprises a composite of mineralized collagen fibrils, amorphous calcium phosphate and crystalline hydroxyapatite, and wherein the crystals of the crystalline hydroxyapatite have a length of about 300 to 500 nm.

Claims 5-6 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 11-047259 in view of Constantz et al (5,279,831) optionally in view of Lussi et al (5,167,961) in further view Sauk et al (4,780,450).

The deficiencies of JP 11-047259, Constantz and Lussi are discussed above. Sauk et al. does not cure these deficiencies.

Sauk et al. teaches a porous composition comprising polycrystalline calcium phosphate ceramic, a phosphophoryn calcium salt and type I collagen for application in osseous repair. Sauk et al. does not teach or suggest a mineralized collagen matrix comprising mineralized collagen fibrils, amorphous calcium phosphate and hydroxyapatite crystals having a length between about 300 to 500 nm. Thus, the combined disclosures of JP 11-047259, Constantz et al., Lussi et al. and Sauk et al. fail to suggest a mineralized collagen matrix as recited in Applicants' claims.

Claims 7 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 11-047259 in view of Constantz et al (5,279,831) optionally in view of Lussi et at

(5,167,961) in further view of Geistlich et al (5,573,771).

The shortcomings of JP 11-047259, Constantz and Lussi are discussed above.

Geistlich et al. (US 5,573,771) teaches a purified particulate bone mineral product, the particles of which may be coated or impregnated by a macromolecular material like, e. g., collagen or gelatin (cf. abstract and column 2, lines 11 to 33). To enhance the binding between the particles and the macromolecule material, the macromolecular material may be cross-linked.

As in the case of Lussi et al. discussed above, Geistlich et al. relates to a product which is made from organic (ex vivo) starting material, i.e., bone product. Thus, one skilled in the art confronted with the problem of manufacturing a synthetic implant coating for metallic implants would never have taken Geistlich et al. into account as being potentially relevant to solve his problem. Like Lussi et al., Geistlich et al. is non-analogous prior art.

Furthermore, the teaching of coating or impregnating a material consisting of a bone mineral by a macromolecule (as derivable from Geistlich et al.) would not lead one skilled in the art to the present invention. Thus, the disclosures of JP 11-047259, Constantz et al., Lussi et al. and Geistlich et al. fail to describe or suggest a mineralized collagen matrix as recited in Applicants' claims.

Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over JP 11-047259 in view of Constantz et al (5,279,831) optionally in view of Lussi et al (5,167,961) in further view of Liu (6,300,315).

The shortcomings of JP 11-047259, Constantz and Lussi are discussed above.

Liu et al. describes a mineralized collagen membrane and a method of making the same. The membrane comprises a homogeneous mineralized collagen composite of 30 to 70 wt% of a collagen component and 30 to 70 wt% of a calcium phosphate component. The membrane is produced by precipitation of calcium phosphate mineral in collagen slurry by maintaining a pH of at least 7.0. Liu utilizes electrolyte solutions of different salt concentrations which result in the formation of different calcium phosphate-collagen compositions. As noted in Example 1 of Liu, the precipitation of calcium phosphate mineral is induced immediately after mixing a 500 mM calcium ion containing solution and a 500 mM phosphate ion containing solution to the collagen slurry at a pH of about 9. This results in the immediate precipitation of calcium phosphate. Such an immediate precipitation of calcium phosphate does not promote the formation of calcium phosphate crystals directly on the collagen fibrils. Thus, only a very loose network of calcium phosphate crystals and collagen fibrils is formed. Moreover, Liu does not disclose or suggest the use of hydroxyapatite crystals having a length of about 300 to 500 nm. Thus, the disclosures of JP 11-047259, Constantz et al., Lussi et al. and Liu. fail to describe or suggest Applicants' claimed invention.

Claims 1, 3-5, 8, 10-16, 18-19, 21, 23-25, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Worch et al (6,524,718) in view of Liu (6,300,315) in further view of Lussi et al (5,167,961). Additionally, Claims 1, 3-5, 8, 10-16, 18-19, 21, 23-25, and 27 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-23 of U.S. Patent No. 6,524,718 (Worch et al) in view of in view of Liu (6,300,315) in view of Lussi et al (5,167,961).

Worch et al. describes a metallic object with a polyphase oxide coating having a metal oxide phase and at least one other organic and/or inorganic phase. The organic phase can contain collagen and the inorganic phase can contain calcium phosphate. Due to the anodic coating process the inorganic and/or organic phase are embedded or incorporated into the metal oxide phase of the implant. The inorganic phase does not form multiple layers on the implant surface.

One skilled in the art would find no teaching or suggestion in Worch of an implant coated with a mineralized collagen matrix comprising mineralized collagen fibrils, amorphous calcium phosphate and hydroxyapatite crystals with a length between about 300 to 500 nm. Additionally, as described above, neither Liu nor Lussi et al disclose or suggest an implant content with a mineralized collagen matrix as recited in Applicants' claims. Thus, combining the teachings of Worch et al., Liu and/or Lussi et al. would not lead a person skilled in the art would to arrive at the implant of the present invention.

Furthermore, at page 15 of the Office Action, the Examiner states that "Worch and Liu do not teach the instant particle size and thus the examiner relies on Lussi et al." However, as previously noted, Lussi teaches a skilled worker away from choosing the instant particle size.

Also on page 15 of the Office Action, the Examiner asserts that, "the definition of adhered is to: To stick fast by or as if by suction or glue. To cause to adhere; make stick." The examiner points out that term "adhered to" does not exclude embedding since embedding is a way of joining (sticking) two surfaces together.

Applicants strongly disagree. "Adhere to said implant surface" is clearly distinguishable from "embedding" which according to Merriam Webster means "to make something an integral part of" (resulting in the surrounding mass being at all sides of the embedded material), while "adhering to a surface" inherently means "to fix onto a surface." Worch et al. explicitly discloses that an organic and/or inorganic component is to be incorporated into a metal oxide phase (column 2, line 55 to column 3, line 3).

Further, at page 15 of the Office Action, the Examiner alleges that in the present application on page 7 (lines 26 to 37) " states that the coating the metallic implant may be done in the process disclosed in WO 98/17844". However, what Applicants' specification clearly

states is that the metallic implant " can have any desired surface geometry..., a chemical modification..., a protein layer and a layer proposed according to WO98/17844." This disclosure does not provide any support for the Examiners assertion regarding "adhered to" or using the process of WO98/17844 to form Applicants' mineralized collagen matrix.

Claims 1, 3-4, 10-16, 18-19, 21, 23-25, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shirkanzadeh (5,205,921) in view of Liu (6,300,315) in further view of Lussi et al (5,167,961) and Claims 6 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shirkanzadeh (5,205,921) in view of Liu (6,300,315) in view of Lussi et at (5,167,961) in view of Sauk et al (4,780,450).

Shirkanzadeh describes an electrochemical process for depositing bioactive coatings, such as calcium phosphate or aluminum oxide, onto conductive substrates. An electrolyte bath containing an aqueous solution of the desired oxide or phosphate is prepared with an inert anode. A titanium implant may be used as the cathode. The electrolyte may further contain collagen. At Examples 1-5 of Shirkanzadeh it is noted that the calcium phosphate coating layer is characterized by either micro pores or is without pores. At col.3, lines 46-48 of Shirkanzadeh, it is pointed out that the micro pores of the calcium phosphate layer encourage adhesion of macro molecules, such as collagen.

As previously discussed, Shirkanzadeh discloses calcium phosphate crystals of 2-5 μm (Example 2) and 20 μm (Example 1). Such crystals are too large to promote a mineralized collagen matrix. Thus, the collagen component of Shirkanzadeh is not mineralized with a calcium phosphate phase and does not resemble native bone material or form a mineralized collagen matrix.

As the Examiner notes on page 18 of the Office Action, the reference (Shirkansadeh) does not teach the combination of amorphous calcium phosphate and hydroxyapatite (1-IA) or the instant particle size of HA. For this, the Examiner relies on Lui et al. or Lussi et al. However, dispersed particles of calcium phosphate mineralized collagen, as taught by Liu, cannot be

precipitated in the electrochemical process of Shirkanzadeh. An electrochemical precipitation process requires imperatively charged particles. A calcium phosphate mineralized collagen according to Liu does not possess an electrical charge anymore. Therefore, the migration and precipitation in an electrochemical process would be strongly hampered and would not provide a coated implant according to the invention. As for the Examiners reliance on Lussi et al., as noted above, Lussi et al. leads one away from choosing a particle size in accordance with the invention.

Thus, the combined teachings of Shirkanzadeh, Liu et al and Lussi et al would not lead one skilled in the art to an implant with the features of the claimed invention. Shirkanzadeh only teaches a method for forming a single layer of hydroxyapatite on the surface of a metallic implant, Liu et al. is silent regarding a metal surface of a metallic implant and Lussi teaches away from selecting the particle size of the instant invention. Shirkanzedah, Liu and Lussi et al. are particularly silent regarding a multilayered coating whereby at least one layer comprises mineralized collagen fibrils, amorphous calcium phosphate and hydroxyapatite crystals having a length of about 300 to 500 nm, particularly since as noted above, Lussi teaches away from the choice of crystals having a length of about 300 to 500 nm.

Thus, the combined teachings of the cited prior art, if taken together, would, at best, only lead a skilled worker to a mixture of collagen and calcium phosphate or hydroxyapatite not to a mineralized collagen matrix as a coating for a metallic implant according to the invention. As discussed above, a mineralized collagen matrix (according to the invention) has a structure that is different from that of a simple mixture of calcium phosphate and collagen. Based on the above remarks is respectfully requested that the rejections under 35 USC §103 be withdrawn.

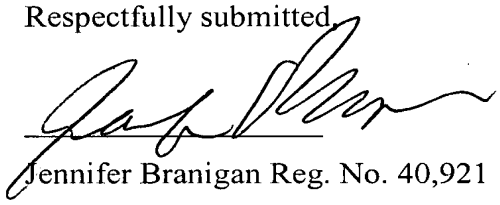
For the Examiners convenience copies of Shirkanzadeh (J. Mat. Sci: Mat. Med., 1998, 9, 67-72) and the excerpt of Lehninger's "Principles of Biochemistry" are re-submitted herewith.

In view of the amendments and above remarks, favorable consideration is courteously requested. However, if there is any remaining issue(s) which can be expeditiously resolved by a

telephone conference, the Examiner is courteously requested to telephone the undersigned at the number indicated below.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,



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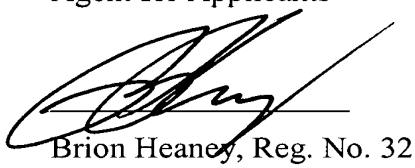

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